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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors:	BIEL, Merrill A.	)	**Attorney Docket No.: 22,272-14**
Serial No:	09/514,070	)	Art Group Unit: ~~3737~~
Filing Date:	February 26, 2000	)	Examiner:
Title:	Photodynamic Therapy Utilizing a Solution of Photosensitizing Compound and Surfactant	)	Transmittal

Assistant Commissioner of Patents
Washington, D.C. 20231

TRANSMITTAL

Sir/Madam:

Enclosed for filing please find the following:

1. Information Disclosure Statement (2 pages);
2. Form PTO-1449 (2 pages) and attached documents cited; and
3. Return Receipt Post Card.

Please charge any further fees necessitated by this correspondence to Deposit Account 12-0449.

Please direct any questions or comments to John F. Klos at (952) 896-1520.

Respectfully submitted,

Date: January 9, 2001. By: John Klos

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Brenda Gunderson: _____
Signature

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BET 1.31.01 #2 IDS

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: BIEL, Merrill A.

Serial No: 09/514,070

Filing Date: February 26, 2000

Title: Photodynamic Therapy Utilizing a Solution of Photosensitizing Compound and Surfactant

Attorney Docket No.: 22272-14

Art Group Unit: 3737

Examiner:

Transmittal

Commissioner of Patents & Trademarks
Washington, D.C. 20231

INFORMATION DISCLOSURE STATEMENT

Pursuant to 37 CFR §1.97 or §1.98, Applicant in the above-identified application submits this Information Disclosure Statement together with the enclosed form PTO-1449 in order to bring to the Examiner's attention references of which Applicant is aware and which may have some bearing on the examination of this case. A copy of each of the identified prior art items is submitted herewith.

This Information Disclosure Statement is not to be construed as a representation that a search has been conducted by Applicant or that no other material information exists. See 37 CFR §1.97(b). Furthermore, statements describing a particular reference indicate only Applicant's understanding of the teachings of that reference, and are not a representation that the reference has been reviewed completely or that no other pertinent or material information is contained in that reference.

Heitz et al., U.S. Patent No. 5,676,959:

This patent purportedly discloses an *ingestible* phototoxic insecticidal composition including a photoactive dye, an attractant compound and/or feeding stimulant, and an adjuvant, whereby the adjuvant interacts with the photoactive dye and insect gastrointestinal (GI) tract to facilitate transport of the phototoxic insecticide *across the GI tract*. The use of an adjuvant to facilitate pharmaceutical uptake *via GI tract absorption* is known in the art. Unlike the surface

acting agents of the Applicant's present invention, these adjuvants do not produce a disorientation of a *cell membrane* so that the *cell membrane* no longer functions as *an effective osmotic barrier*.

Abstract: "The phototoxic insecticidal composition includes at least one photoactive dye present in the amount of between 0.025% - 4.0% of the composition, an attractant compound and/or feeding stimulant and at least one adjuvant, whereby the adjuvant interacts with the photoactive dye and insect membranes to alter the toxicity of the composition once *ingested by the insect*." (Emphasis added).

"The present invention is directed to an insecticidal composition which combines one or more selected photoactive dyes with a selected attractant (bait) and a selected adjuvant wherein *the selected adjuvant interacts with the insect membranes to alter the transport of the dyes through the insect body to susceptible target organs*. Accordingly, through specific interactions of the photoactive dye, the selected adjuvant, and the insect membranes, there is a significantly increased, controllable and previously unknown toxic effect that results in mortality of the particular targeted insect." Column 2, lines 55 – 65. (Emphasis added).

"Inactivation of Gram-Negative Bacteria by Photosensitized Porphyrins" Nitzan, et al., Photochemistry and Photobiology, Vol. 55, No. 1, 1992.

This article purportedly discloses the use of polycationic agent polymyxin nonapeptide (PNMP) in association with a photoactive agent, deuteroporphyin (DP). PNMP is disclosed to disturb the outer membrane of a gram-negative bacteria so as to permit access of the DP to *bind to* the internal lipoprotein osmotic membrane of the bacterial cell. PNMP is disclosed to only disturb the outer membrane structure *and not its function, and not cause metabolic leakage from the cells (or osmotic changes in the cell)*. Unlike the surface acting agent of the Applicant's present invention, PNMP does not produce a disorientation of a *cell membrane* so that the *cell membrane* no longer functions as *an effective osmotic barrier*. In the Applicant's present invention, the surface acting agent causes a disorientation of the cell membrane thereby compromising the effective osmotic membrane barrier and thus allowing the photosensitizer to diffuse through the compromised cell membrane into the cell.

Abstract: "Photosensitzation of Escherichia coli and Pseudomonas aeruginosa cells by deuteroporphyin (DP) is shown to be possible in the presence of the polycationic agent polymyxin nonapeptide (PMNP). Previous studies established complete resistance of Gram-negative bacteria to the photodynamic effects of porphyrins. The present results show that combined treatment of E.coli or P. aeruginosa cultures with DP and PMNP inhibit cell growth and viability. *No antibacterial activity of PMNP alone could be demonstrated and cell viability remained unchanged.* Spectroscopically, PMNP was found to bind DP, a mechanism which probably assists its penetration into the cell's membranes. Insertion of DP into the cells was monitored by the characteristic fluorescence band of bound DP at 622 nm." Lines 1 – 8 (emphasis added).

"One of the prerequisites for the photodynamic killing effect to take place is *the binding of the porphyrin molecule to the bacterial cell* (Malik, et al., 1982). Specifically, it was found that *the binding must be to the cell membrane* (Ehrenberg, et al., 1985). Florescent studies have indicated that the complex cell wall of Gram-negative bacteria shields the cytoplasmic membrane and thus prevents porphyrins from binding to the membrane. Removal of the cell wall and formation of spheroplasts increased the binding of porphyrins to the cell membrane (Ehrenberg, et al., 1985)." Page 89.

"We demonstrate the spectral effects of the interaction between DP and the permeabilizing agent polymyxin nonapeptide (PMNP). PMNP is a disorganizing nontoxic agent of the bacterial membrane structures (Vaara and Vaara, 1983b; Lam, et al., 1986). We studied, spectroscopically, the uptake of DP by bacterial cells and the effect of pH, PMNP and the concentrations of cells on the binding. Based on the spectroscopic evidence of DP uptake, growth inhibition, decrease in viability and ultrastructural changes it is demonstrated that in the presence of PMNP even Gram-negative bacteria can be photo-sensitized very efficiently by metal-free porphyrins." Page 89.

"All this has led to the conclusion that in Gram-negative bacteria photosensitization will be possible only by a disturbance in the cytoplasmic membrane's structure. Recently, it has been shown (Bertoloni, et al., 1990) that alterations of the outer membrane induce photosensitivity in E. coli to phthalocyanines." Page 94.

"The main advantage of using PMNP was that it is a moderate agent, acting on the growing bacteria in their natural environment in the culture media. *It seems from the results that PMNP alone only disturbs the membrane structure and not is function, and does not cause metabolic leakage from the cells.*" Page 94 (emphasis added).

"It is clear that PMNP disturbs and disorganizes the outer-membrane structure of Gram-negative bacteria, as shown previously by others (Vaara and Vaara, 1983 a, b). In our case without such a *disturbance of the outer membrane, DP cannot act on the inner membrane of these bacteria.*" (emphasis added), Page 95.

Lyons, U.S. Patent No. 5,616,342:

This patent purportedly discloses an emulsion comprising a lipid, a poorly water-soluble photosensitizing compound, a surfactant, and a cosurfactant. Poorly water-soluable photosensitizers are disclosed to pose serious challenges to achieving suitable formulation. Column 1, 60-61. Surfactants facilitate the preparation of the emulsion by stabilizing the dispersed droplets of an oil-in-water emulsion. Column 2, lines 22 – 24. The use of surfactants in combination with poorly water-soluable pharmacologic compounds is known in the art. Unlike the surface acting agents of the Applicant's present invention, the surfactant in Lyons '342 does not produce a disorientation of a *cell membrane* so that the *cell membrane* no longer functions as *an effective osmotic barrier*.

Applicant's submittal of these references is not to be construed as an admission that these references are prior art or material to the patentability of any pending claim.

Applicant's discussion in this IDS or the Background of the specification is not to be construed as an admission that these references are prior art, material to the patentability of any pending claim, or any more material than the prior art listed on PTO-1449.

In the event that this Information Disclosure Statement was mailed after the mailing date of the first Office Action on the merits in the above-captioned application, please charge any fee of surcharge necessary for the consideration of this Information Disclosure Statement and

enclosed form PTO-1449 to the deposit account of the undersigned firm of attorneys, Deposit Account 12-0449, and notify the undersigned of such charge.

Please direct any questions or comments regarding this application or Information Disclosure Statement to John F. Klos at (952) 896-1520.

Respectfully submitted,

Date: January 9, 2001

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Brenda Gunderson: _____
Signature

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